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ALSTON & BIRD LLP
BANK OF AMERICA PLAZA
101 SOUTH TRYON STREET, SUITE 4000
CHARLOTTE, NC 28280-4000

EXAMINER	
KUBELIK, ANNE R	

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RECORD OF ORAL HEARING

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte ANDRE R. ABAD, et al.

Appeal 2007-4213
Application 10/032,717
Technology Center 1600

Oral Hearing Held: March 12, 2008

Before DONALD E. ADAMS, ERIC B. GRIMES, and JEFFREY N. FREDMAN, *Administrative Patent Judges*.

ON BEHALF OF THE APPELLANTS:

W. MURRAY SPRUILL, Ph.D., ESQ.
Alston & Bird, LLP
3201 Beechleaf Court, Suite 600
Raleigh, North Carolina 27604-1062
(919) 862-2202
murray.spruill@alston.com

The above-entitled matter came on for hearing on Wednesday, March 12, 2008, commencing at 1:53 p.m., at the U.S. Patent and Trademark Office, 600 Dulany Street, Alexandria, Virginia, before Dawn A. Brown, Notary Registration No. 7066896, Notary Public.

THE CLERK: This is Calendar Number 25, Appeal 2007-4213 and 2007-4356. The attorney is Mr. Murray Spruill.

JUDGE ADAMS: Good afternoon, Mr. Spruill.

MR. SPRUILL: Good afternoon.

JUDGE ADAMS: We're familiar with the issues. We're going to handle both of these cases at the same time so we don't bother you with walking in and out one after the other. And you have 20 minutes. And you can begin by introducing and spelling your name for the record.

MR. SPRUILL: Good afternoon. May it please the Court, my name is Murray Spruill, S-P-R-U-I-L-L, and I'm here representing Pioneer Hi-Bred in the above cases. As you indicated, these are two related cases. The issues are essentially identical in both cases. We are claiming two sequences, two nucleotide sequences in each of these cases.

The invention in both of these cases are drawn to novel *Cry*8-like endotoxins or nucleotide sequences, which encode these *Cry*8-like endotoxins. The endotoxins are insecticidal. These two nucleotide sequences were isolated from a *Bacillus* strain, which was shown to have insecticidal activity.

When the proteins were isolated from that *Bacillus* strain and then tested for activity, these two proteins were indicated and shown to be insecticidal. The interesting thing about these are these two proteins or these two nucleotide sequences that encode the proteins are natural variants of one another.

That is, the nucleotide sequence, both of these share about between 92- and 93-percent sequence identity to each other. The encoded polypeptides share about 89-percent sequence identity.

In the claims in both cases, the claims are drawn to nucleotide sequences. They're drawn to methods for using these nucleotide sequences and for plants encoding these nucleotide sequences.

And in addition to the specific nucleotide sequences, we have claims that are drawn to nucleotide sequences having a percent identity to our SEQ ID 1 and SEQ ID 3.

The claims in both cases or some of the claims in both cases have been found to be rejected by the examiner for lack of enablement and for lack of written description.

If we begin with the enablement, the examiner has indicated that while the claims are enabled for our exact sequences, they are not enabled for our claims that are drawn to percent identity.

And if we look at the standard for enablement, as you know, we look to what the specification teaches. The specification must teach the skilled artisan to make and use the full scope of the claimed invention without undue experimentation.

So we do an analysis of the specification, and then we look into what a person of ordinary skill in the art would know. What is the knowledge in the art?

If we began by looking at the teachings of our specification, the specification provides nucleotide sequences that show where modifications can be made and nucleotide sequences obtained that fall within the scope of the claims, they obtain guidance regarding alterations that can be made to allow the amino acid sequence to retain pesticidal activity.

We have methods for assaying the insecticidal activity of protein in our specification. And we have examples that also teach how to

assay for the insecticidal activity.

We have a discussion of *Cry*8-like endotoxins, so the discussion is concerning the structure of these *Cry*8-like endotoxins. And we have guidance for determining percent identity between nucleotide sequences. In addition, we have specific mutations that fall within the scope of our claims.

JUDGE GRIMES: When you refer to the guidance as to which changes can be made, could you point us to the specific part of the specification you're referring to?

MR. SPRUILL: Yes. If you look in the specifications, we talk about the description of our mutagenized variants, which provide guidance for where one would go to make changes. I'm looking at the published application. We begin there at paragraph 71 through 75. Methods for mutagenesis we begin discussing on paragraph 85.

The conserved regions within the Bt is discussed beginning at paragraph 88. And at paragraph 89, we talk about analyzing the structure of Bt endotoxins to determine target sites for mutagenesis.

Paragraph 90 discusses using homology models to determine the relationship between structure and to design engineered proteins, and in particular, one of the things that we did or the inventors did in this case was to target a region that was located between the alpha-helices 3 and 4 of domain 1, which was known to be involved in toxicity and that begins at paragraph 91.

And then beginning at paragraph 94, we describe our particular mutations.

And if you also look at our appeal brief at Appendix A,

Appendix A in both instances contains a chart, which provides our variants that we have made, and then provides whether those variants retain activity, provides local and global percent identity of those variants against SEQ ID number 1 and SEQ ID number 3.

If we look at what these variants are, first of all, truncations have been made. Truncations have been made in the 3' region of the polypeptide and in the 3' and 5' regions of the polypeptide.

And then within some of these truncations, we've made additional amino acid changes to change that cleavage site that I mentioned earlier that we discussed at about paragraph 94.

In particular, I'd like to call your attention to truncation and variant, which is SEQ ID number 9, because if we look at SEQ ID number 9, that has deleted over a third of our SEQ ID number 1 or 3 -- SEQ ID number 1 and 3 contain about 3,600 nucleotides; SEQ ID number 9 contains about 2,000 nucleotides and encodes about 669 amino acid sequence.

So we see there that what we say we teach is a critical region would be this region within the variant that is shown in SEQ ID number 9.

Even within SEQ ID number 9, if you compare SEQ ID number 9 with SEQ ID number 3 -- and we make that comparison because when the inventors made our variants, they used SEQ ID number 1. And we told you that SEQ ID number 3 is a natural variant of SEQ ID number 1.

So by comparing SEQ ID number 9 with SEQ ID number 3, we find additional variations within our truncated region that we know that can be changed. If you make that change within the 669 truncated amino acid sequence, you see 131 amino acid changes in that it is 94 substitutions, 20 deletions, and 17 additions.

It is about 20 percent of that smallest variant that can still be modified, can still be altered, and retain activity.

JUDGE ADAMS: Let me make sure I understand this. We have, essentially, three domains; is that right?

MR. SPRUILL: That is correct.

JUDGE ADAMS: We can pretty much just get rid of domains 2 and 3 and still have activity.

MR. SPRUILL: Domains 2 and 3 are still present. As the examiner has pointed out, a lot of times the 3' or 5' region of the protein is not used. In fact, a truncated protein can be used, but what we've done is provide additional truncations at the 5' and some at the 3'.

JUDGE ADAMS: For all intents and purposes you can retain activity if you get rid of the second and third domain.

MR. SPRUILL: No, you need the second and third domains. The second and third domains are important for enzyme specificity. These endotoxins recognize particular insects.

JUDGE FREDMAN: What is being deleted? Wouldn't that be the first, second, or third domain?

MR. SPRUILL: When the endotoxin is processed within the insect gut and the C terminal region is clipped off; in fact, that is why you can use a truncated portion of this, and, in fact, why they knew they could truncate a large part of SEQ ID number 1 and 3 and still retain activity.

JUDGE FREDMAN: What is the C terminal? Which domain is that?

MR. SPRUILL: It is not domain 1, 2 and 3. Domains 1, 2, and 3 are involved what is called the toxin part. That is part of the protoxin. It is

a proenzyme.

JUDGE ADAMS: We can make modifications to the to 5' --

MR. SPRUILL: That is correct. We deleted portions of that. And we've also made within our truncations, within the regions that remain, we've put additional protease sites within that. We've made deletions and additions and substitutions of the nucleotide sequences there.

JUDGE FREDMAN: The De Maagd reference discusses how -- assuming I'm reading correctly -- affect specificity for insects.

MR. SPRUILL: That is correct. And if you look at the De Maagd reference, what they were doing there is trying to determine the specificity for army worm and by doing that they were looking at domain 3 from *Cry*1-C and *Cry*1-E. *Cry*1-C has activity again, the army worm. The *Cry*1-C does not have specificity toward that, so they align these sequences.

And in aligning Bt's, as you see in figure 3, even though they don't have the same specificity for the insect, you're going to find regions of homology. The Bt endotoxins have been widely studied and there are core regions known within these.

To me, it is not surprising that when they align *Cry*1-C and *Cry*1-E they see differences and can make changes in those nonconserved which affect specificity. I would expect that. The specificity for those endotoxins is not the same.

That brings us to the knowledge in the art. I think the prior art originally cited by the examiner and which we relied on in our brief as well, the De Maagd as well as the other two Bt articles, would tend to show it is routine in the art to make mutations within these endotoxins and then test those endotoxins for activity.

Appendix C of our brief is a declaration by of skill in the art, an employee of Pioneer Hi-Bred, who indicated in her opinion it was within the skill of one in the art to make and test these mutants.

So with all of that, with the teachings that we provided, the mutants we provided, and with the knowledge of skill in the art, we believe we've readily enabled claims to 90-percent identity and in the SEQ ID 1, 93, 94, 95, and in SEQ ID 3 to, at least, 95 percent.

So then if we move to written description, as you know, the standard for a written description is that the written description for genetic material provides a precise definition whether by structure, formula, chemical name. And so the goal is to clearly convey that we were in possession or the inventors were in possession of the invention at the time the application was filed.

So we look.

JUDGE FREDMAN: So you're teaching the structure-function relationship?

MR. SPRUILL: Yes. I think we have taught the structural-function relationship. As the examiner has pointed out, there are many modifications, many variants that fit within the scope of our claims. We've shown some.

We don't believe we have to show all of them because we've shown a structure-function relationship and that structure-function relationship is best seen beginning with SEQ ID number 9, which shows that a small portion of our SEQ ID numbers 1 and 2 can be deleted and you retain activity.

And then again within SEQ ID number 9 itself, the 131 amino

acids -- the 131 amino acids that could be deleted, or substituted or deleted within that region, and so we think that we have shown a clear structure-function relationship for our SEQ ID 1 and 3 that one skilled in the art would readily be able to determine that we were in possession of the claimed invention.

Again, the chart, we believe, helps us. That is some variants we provided and we've shown the percent identity there.

JUDGE FREDMAN: How do you address the examiner's point that there are a very large number of numbers of this genus? 19 to the --

MR. SPRUILL: 19 to the 36 thousand and -- that is, yeah. Because she is changing one amino acid at a time and that is true.

JUDGE FREDMAN: And within the scope of the claims.

MR. SPRUILL: That is correct. We don't dispute it is a large number that would fall within the scope of the claim. We believe, though, if you look at our specification and if you study the variants that we've shown, we teach a large number of mutations that can be made and retain activity.

And we don't believe that we have to teach every variant that would fall within the scope of the claims. But we have to be able to lead one skilled in the art to make decisions about that. Which we think we've done.

Not only that, but what was known in the art about Bt's, the general structure of Bt's were known as De Maagd showed. When even Bt's of cross-classes are aligned, you find conserved regions. We would teach staying outside of the conserved regions to make any changes.

JUDGE FREDMAN: How does the crystal structurally relate to this? Is it a related protein?

MR. SPRUILL: Well, it is a crystal protein. The Bt endotoxins

are crystal proteins. They're solubilized in the insect gut. Their process there, the protease cleave, which is why we were adding protease sites to increase toxicity. And then there is a pore-forming domain, which is domain 1, which is responsible for toxicity, and the other two domains help.

JUDGE GRIMES: Would it be reasonable to conclude based on your deletion studies that any substitutions within those regions that you showed could be deleted without affecting function?

MR. SPRUILL: Could be deleted without changing function.

JUDGE GRIMES: They could also be substituted?

MR. SPRUILL: We believe if you make conservative substitutions, you're less likely to change, but I do think the examiner has a point. The examiner indicates that you have to be careful, even in those regions where we deleted, because if we put the complete protein in, then you have to pay attention to the 3D structure of the protein.

So while we believe you can more readily make changes in those regions, you would still have to test those for activity.

So with the showing that we've made, we believe one skilled in the art would recognize that we were in possession of the invention. If you lack at our variants, some of them are well below the claimed 90 percent.

You mentioned the references. One of the references that the examiner has cited against us to show that the conservative changes don't always lead to changes in binding or specificity, but we would encourage you to do a close reading of those references.

For example, if you look at the Lazar reference, that reference was designed to find an antagonist for TGF alpha. So they looked at conserved amino acids within that family. They mutagenized these two

conserved amino acids because they expected these conserved amino acids would play a role in binding and in the cellular transduction or signaling that happens with it.

It was more surprising that one of them didn't show, you know, that much correlation. What was not surprising was that you could change one even to a conservative amino acid and you have an effect on it. The art would teach that is why they went after conserved amino acids. One expects those to play a role in binding or in activity of the enzyme.

Lastly, I would ask that you consider fairness. Something that you can't ask the examiner for; well, we can ask. But I would ask that you consider fairness because we have taught these sequences, we taught modifications that can be made to these sequences, and we taught deletions that can be made to these sequences.

And in return, to reward us with a patent to just the sequence itself because you've seen it is so easy to make changes within amino acid and protein sequences and get around the claim of the scope. We think a scope of 90 percent, we should be entitled to in all fairness.

And we've looked at -- and I know each case is examined on its own merits. But, again, we would ask that you would be fair to us. In the Bt area there is a few examples.

In fact, there is one which shows a plant, which is transformed with a nucleic acid having at least 50-percent identity to a nucleic acid sequence, and they have no examples of variants and no examples in that specification. But they go up to 90 percent and, of course, to the sequence.

Other plant enzymes range from 60 to 90 percent. So within that setting, we believe that we have demonstrated regions that one could

mutate and retain activity, so we've fulfilled the enablement standard because it would be within the skill of the art to make those changes and test it.

JUDGE FREDMAN: If you look at Kubin, obviously, the decision was a case of enablement where enablement was reversed in view of the facts.

MR. SPRUILL: Exactly.

JUDGE ADAMS: Anything else for us?

MR. SPRUILL: I think that is it. Thank you very much.

JUDGE ADAMS: Any questions?

Thank you very much.

(Whereupon, the proceedings at 2:14 p.m. were concluded.)